IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	10/084,676	Confirmation No. :	2539
First Named Inventor	:	Iris ZIEGLER		
Filed	:	February 28, 2002		
TC/A.U.	:	1618		
Examiner	:	Blessing Fubara		
Docket No.	:	029310.50932		
Customer No.	:	23911		
Title	:	Oral Pharmaceutical Forms of Administration with a Delayed Action		

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Mail Stop: **Appeal Brief- Patents**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The following Appeal Brief is submitted further to Applicants' October 11, 2007 Notice of Appeal to the Board of Patent Appeals from the July 11, 2007 final rejection of claims 17 and 38. An extension of the deadline for filing this brief is respectfully requested pursuant to 37 C.F.R. § 1.136(a) and the appropriate fee is submitted herewith.

REAL PARTY IN INTEREST (37 C.F.R. § 41.37(C)(1)(I))

The real party in interest in this Appeal is the assignee Gruenenthal GmbH, a German Company having an address at: Zieglerstrasse 6, D-52078 Aachen, Germany, as reflected in the assignment recorded with the U.S. Patent and Trademark Office at Reel/Frame 012919/0535 on May 22, 2002.

RELATED APPEALS AND INTERFERENCES (37 C.F.R. § 41.37(C)(1)(II))

Appellants are not aware of any interferences or other appeals that would affect, be affected by, or have a bearing on a decision in this appeal.

STATUS OF CLAIMS (37 C.F.R. § 41.37(C)(1)(III))

Independent claims 17 and 38 were finally rejected in the Final Office Action mailed July 11, 2007. Claims 1-16 and 18-37 were cancelled in the response filed July 28, 2003.

STATUS OF AMENDMENTS (37 C.F.R. § 41.37(C)(1)(IV))

No amendment was filed subsequent to the final rejection, and there are no unentered amendments in the application.

SUMMARY OF THE CLAIMED SUBJECT MATTER (37 C.F.R. § 41.37(C)(1)(V))

Independent claim 17 is directed to a sustained-release, oral pharmaceutical formulation of tramadol, comprising a compound of tramadol hydrochloride and diclofenac sodium.

This pharmaceutical formulation is described in the specification on page 2, beginning at line 24 and continuing on to page 4, line 27.

Independent claim 38 is directed to a process for preparing an oral pharmaceutical formulation comprising the steps of:

mixing tramadol hydrochloride and diclofenac sodium to form a mixture;

moistening the mixture; and

repeating the above mixing and moistening steps and formulating the mixture under an energy input.

This process is described in the specification beginning on page 7, line 26 and continuing on to page 8, line 2 and then continuing on page 8, at lines 21-23.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL (37 C.F.R. § 41.37(C)(1)(VI))

The grounds of rejection to be reviewed on appeal are:

(i) whether claim 17 is indefinite under 35 U.S.C. § 112, second paragraph;

(ii) whether claim 17 is anticipated, under 35 U.S.C. § 102, by Mauskop (U.S. Patent No. 5,914,129); and

(iii) whether claim 38 is obvious, under 35 U.S.C. § 103, over Mauskop (U.S. Patent No. 5,914,129).

ARGUMENT (37 C.F.R. § 41.37(C)(1)(VII))

I. The Examiner Improperly Rejected Claim 17 Under 35 U.S.C. § 112, Second Paragraph For Indefiniteness.

The Federal Circuit has said that "[t]he statute is satisfied if a person skilled in the field of the invention would reasonably understand the claim when read in the context of the specification." *Marley Mouldings Ltd. v. Mikron Industries Inc.*, 75 USPQ2d 1954 (Fed. Cir. 2005). The Federal Circuit has also said that § 112 demands no more than that the claims "reasonably apprise those skilled in the art of the scope of the invention." *Miles Labs., Inc. v. Shandon*, 27 USPQ2d 1123 (Fed. Cir. 1993). In the present instance, a person of skill in the art could readily understand claim 17 and determine the scope of the invention. Accordingly, claim 17 satisfies the requirements of 35 U.S.C. § 112, second paragraph.

The law does not require a chemical compound claim to recite the specific structure of the compound. *See, e.g.*, MPEP, at § 2173.05(t) "[a] claim to a chemical compound is not indefinite merely because a structure is not presented or because a partial structure is presented." Indeed, one Court held a claim not indefinite where that claim was directed to a nonionic complex of ferric hydroxide with a dextran. The claim did not describe any structure; instead, it only required a viscosity within a certain range and that the complex be stable in contact with water. The Court held that:

> The precise chemical structure of the claimed product is not known to either the plaintiff or the defendants, nor to any of the impressive array of experts whom they called and, being unknown, it is not nor can it be described or claimed by chemical structural formula.

> However, nothing in the law requires the courts to deny a patent to the inventor of a new and useful product merely because laboratory technique has not advanced to a point where the chemical structure can be recognized and described. All that is necessary is that the patentee make as full disclosure as he reasonably can and that he describe the product with sufficient particularity that it can be identified and that those who are interested in its manufacture are enabled to determine what will and what will not infringe.

Benger Labs, Ltd. v. R.K. Laros Co., 135 USPQ 11 at 14 (E.D. Pa. 1962), *aff'd*, 137 USPQ 693 (3d Cir. 1963).

Much like the claim at issue in the *Benger Labs* case, the language of claim 17 specifically recites "a compound of tramadol hydrochloride and diclofenac sodium." This claim language makes it clear that a compound is required. The claim also describes that "said compound" is formed *in situ* and that the compound has a water solubility of ≤100 mg/ml. Thus, the skilled artisan would readily understand that the claim is directed to a *compound* of tramadol hydrochloride and diclofenac sodium and not a simply mixture of these two ingredients. Accordingly, the assertion in the Office Action that claim 17 reads on a simple *mixture* of tramadol hydrochloride and diclofenac sodium is incorrect. To read the language of claim 17 to cover a simple mixture of tramadol hydrochloride and diclofenac sodium improperly requires a complete disregard of the multiple recitations of the word "compound" appearing in claim 17.

Despite this clarity that the claim requires a compound of tramadol hydrochloride and diclofenac sodium, the Examiner asserts that a compound is not formed in accordance with the teachings of the present specification and reads the claim to cover simple mixtures of tramadol hydrochloride and diclofenac sodium.

The Examiner appears to be assigning a meaning to the word "compound" that is well beyond any reasonable interpretation a skilled artisan would give the word. In particular, the Examiner asserts that because the inventive compound can be decomposed to release tramadol and diclofenac, there is actually no compound formed. However, just because the tramadol and diclofenac can be chemically

released does not mean that a compound was not formed. Consider, for instance, the well-known ionic compound commonly referred to as table salt and known chemically as sodium chloride. Sodium chloride will readily dissolve into constituent sodium ions and chloride ions, simply by adding the sodium chloride to water. According to the logic of the Examiner, sodium chloride would not be a compound because it can be dissolved into its constituent ions.

The Examiner relies on Hackh's Chemical Dictionary for the proposition that a compound "cannot be separated by physical means." This language in the reference refers to simple mechanical separation processes, such as filtering by particle size, and not to chemical dissociative processes such as dissolving. Indeed, the Examiner's reading of the definition from Hackh's would mean that there could be only a few instances of "ionic compounds", since most ionic compounds will dissolve in an appropriate solvent. Although a compound can commonly be dissolved into its constituent parts, this does mean that the compound should be considered only a mixture rather than a compound. Moreover, a claim directed to a compound that can be so dissolved does not read on a simple mixture and is not, as a result of this solubility, indefinite in any way.

Further, the Examiner notes that a compound "differs from a physical mixture . . . by the disappearance of the properties of the constituent elements, and, by entirely new properties characteristic of the compound." Thus, the Examiner appears to doubt that a compound is actually formed by the teachings of the present invention. Thus, the trouble the Examiner has is not one of determining the meaning or scope of the claim. Rather it is whether or not a compound is actually formed. Any doubts the Examiner may have as to whether or not a compound is actually formed do not raise an issue of definiteness under 35 U.S.C. § 112.

Supposing that the Examiner's definition of a compound as differing "from a physical mixture . . . by the disappearance of the properties of the constituent elements, and, by entirely new properties characteristic of the compound" is proper, then the declaration evidence already of record in this application presents a

compelling case that a compound is made. In particular, the evidence appearing in Exhibits I and II shows the disappearance of certain properties of the constituent elements of the claimed compound as well as the appearance of certain properties of to the compound. The declaration evidence is discussed further below and shows the person of skill in the art that a compound is formed in accordance with the inventive teachings of this application.

The claim is directed to a pharmaceutical formulation comprising a compound of tramadol hydrochloride and diclofenac sodium. The meaning of this claim language is not in any way unclear. As a result, claim 17 is not indefinite and the language therein satisfies the requirements of 35 U.S.C. § 112, second paragraph.

II. The Examiner Improperly Rejected Claim 17 Under 35 U.S.C. § 102 Over Mauskop (U.S. Patent No. 5,914,129).

As noted above, claim 17 is directed to a compound of tramadol hydrochloride and diclofenac sodium. Mauskop does not disclose any such compound. Mauskop merely discloses compositions comprising a mixture of a non-opioid analgesic selected from a first list of 17 possibilities and an opioid analgesic selected from a second list of 16 possibilities. Mauskop does not even specifically disclose a *mixture* of tramadol hydrochloride and diclofenac sodium. Instead, to arrive at such a mixture, one would have to make certain selections from the lists of possibilities provided in Mauskop. On the present record, there is nothing to cause the skilled artisan to make these certain selections.

Moreover, as explained above, claim 17 does not read on a simple mixture of tramadol hydrochloride and diclofenac sodium. The Examiner's reliance on the proposition that "[p]roducts of identical chemical composition can not have mutually exclusive properties" is misplaced. See, page 6 of the Final Office Action of July 11, 2007. Again, the important distinction is that Mauskop describes simple *mixtures*, whereas the claims and the invention are directed to a *compound* of tramadol

hydrochloride and diclofenac sodium. Thus, Mauskop does not describe a product having an identical chemical composition with that of claim 17.

The declaration of Dr. Iris Ziegler submitted in this application on December 15, 2006 and attached hereto as Exhibit I shows that the inventive teachings of the present application do, in fact, achieve a *compound* of tramadol hydrochloride and diclofenac sodium. In particular, the declaration reports in detail the results of two sets of tests demonstrating that the claimed product of the invention produced by the claimed process of the invention is different from a product produced according to the teachings of the cited Mauskop patent.

The first set of tests shows that the claimed, *in situ* formed compound of tramadol hydrochloride and diclofenac sodium has a distinctly different release profile than a corresponding composition containing a mixture of tramadol hydrochloride and diclofenac sodium produced in accordance with the teachings of Mauskop. The second set of tests confirms through differential scanning calorimetry (DSC) that the claimed product of the invention produced by the claimed process of the invention contains a physical/chemical entity (i.e., an *in situ* formed compound) which is not present in the corresponding composition containing a mixture of tramadol hydrochloride and diclofenac sodium produced in accordance with the teachings of Mauskop. The different release profile and the different DSC spectrum obtained for the claimed compound show that the claimed compound is different from a simple mixture of the two active substances.

In particular page 2 of Dr. Ziegler's declaration describes the preparation of tablets containing a mixture of tramadol hydrochloride and diclofenac sodium. Pages 3 and 4 of the declaration describe the preparation of tablets of the inventive compound of tramadol hydrochloride and diclofenac sodium of present application. Page 4 also describes the test to compare the release profiles of these two different tablet types and page 5 includes a chart showing the results of this test. The release profile curves show a much faster release for the active ingredients from the tablets containing a mixture. Indeed, as described by Dr. Ziegler in the text on page

5, both active ingredients were 100% released within 15 minutes. In contrast, the release profile of the tablets including the inventive compound exhibited a greatly slowed release of the active ingredient. As described by Dr. Ziegler, 600 minutes were required to release 100% of the tramadol. Further, in this time, only 80% of the diclofenac was released. Dr. Ziegler also explained that the similar hardness and disintegration times of the tablets shows that the slower release rate of the tablets having the inventive compound is not a product of different characteristics of the tablets, see the top of page 6. Rather, Dr. Ziegler concludes from this test that the slowed release rate of the tablets including the inventive compound is a result of these tablets being present in different physical and chemical form, i.e., a compound having a lower solubility that then the simple mixture of active ingredients.

Pages 6-9 describe the results of DSC analysis as applied to the inventive compound, as well as a simple mixture of active ingredient. In particular, Exhibits A-E attached to the declaration show the DSC spectra obtained for the tablets containing a mixture of the active ingredient (Exhibit A); tablets containing the inventive compound (Exhibit B); tablets containing a salt of tramadol and diclofenac (Exhibit C); tablets containing a salt of tramadol and diclofenac with added NaCl (Exhibit D); and a simple mixture of the active ingredient (Exhibit E).

As explained by Dr. Ziegler on pages 8 and 9, the various DSC spectra demonstrate that the tramadol and diclofenac in the tablets containing the inventive compound are present in a different physical and chemical form from both the tablets containing the mixture of the active ingredients, as well as the simple mixture of active ingredients that were not tabletted. In particular, Exhibit B shows a pronounced peak at approximately 292°C and this peak is not present in the other spectra. As described on page 9, Dr. Ziegler concludes that these results show that the product of the present invention contains a compound of tramadol hydrochloride and diclofenac sodium and not just a simple mixture.

This evidence is compelling to show that a compound of tramadol hydrochloride and diclofenac sodium is actually formed in accordance with the

teachings of the present application. Based on this evidence, the Board should reject the Examiner's unsubstantiated assertions that a compound is not formed. Moreover, the Board should determined that the anticipation rejection is improper.

III. The Examiner Improperly Rejected Claim 38 Under 35 U.S.C. § 103 Over Mauskop (U.S. Patent No. 5,914,129).

Claim 38 is directed to a method of making the claimed compound formed of tramadol hydrochloride and diclofenac sodium comprising repeated mixing and moistening followed by formulation under an energy input. As noted above, Mauskop merely discloses forming a tablet from a mixture of an opioid analgesic and a non-opioid analgesic. If proper selections were made from the lists of possible analgesics provided by Mauskop, one might arrive at a mixture of tramadol and diclofenac. However, Mauskop does not describe repeating mixing and moistening steps. Rather, the Office Action of July 11, 2007 asserts that repeating these steps is an obvious variant of the prior art methods available to the skilled artisan, see page 8. The Office Action also indicates that Mauskop fails to specifically describe formulation under an energy input, and instead posits that compressing or granulating involves energy input.

The rejection surmises that it would be obvious to repeat the mixing and moistening steps and to formulate under an energy input in order to obtain a desired composition, but the rejection fails to explain why the skilled artisan would be inclined to repeat the above mixing and moistening steps and formulate the mixture under an energy input as is required in claim 38. Neither Mauskop nor any other evidence of record discloses or suggests the possibility that these steps might yield a compound as contemplated in the present application. Nor is there any explanation on the present record of what purpose would be served by repeating the mixing and moistening steps or why a person skilled in the art would find it obvious to go to the trouble and expense to repeat such steps when no purpose would be served.

As pointed out by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 SCt 1727, 82 USPQ2d 1385, 1396 (U.S. 2007), such unsupported conclusory statements cannot sustain a rejection.

> [R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness". (Quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329 (Fed. Cir. 2006) with approval).

Although an explicit teaching, suggestion or motivation need not be found in the cited references, to properly reject for obviousness, it is nevertheless necessary for the Examiner to articulate a convincing rationale as to what would lead a person skilled in the art to depart from the teachings of the prior art and strike out in the new direction claimed by applicants as their invention. This the Examiner has failed to do, and this failure constitutes a clear error in the rejection. It follows that a proper, *prima facie* case of obviousness has not been made out, and the rejection should be withdrawn.

Moreover, even if a *prima facie* case had been made out, it would be rebutted by the declaration evidence of record. The declaration evidence shows that a tablet containing the compound of tramadol hydrochloride and diclofenac sodium produced by the method of the invention has an unexpectedly superior slower release profile compared to a tablet formed from a mixture of tramadol hydrochloride and diclofenac sodium. (See, e.g., paragraph 5.I.(d) of Dr. Ziegler's declaration on page 5). This unexpectedly improved release profile obtained by the claimed invention could not have been expected or predicted based on the teachings of Mauskop or any other prior art of record.

The declaration evidence also shows that the claimed compound of tramadol hydrochloride and diclofenac sodium exhibits a DSC spectrum which is significantly different from that of a simple mixture of tramadol hydrochloride and diclofenac sodium, whether that simple mixture is tested in tablet form or as the simple mixture itself.

Repeating the moistening and mixing steps as recited in claim 38 would not have been obvious to a person of ordinary skill because he/she would not have been aware that purpose might be served by such repetition. It is improper to assume that a skilled worker would find it obvious to carry out steps which serve no purpose. A person of ordinary skill in the art would have had no way of knowing that the repetition of such steps would contribute to the production of an *in situ* formed compound with the unexpected and surprising properties documented in the Dr. Ziegler's declaration. Therefore, the claimed invention is non-obvious and patentable over the Mauskop patent.

CONCLUSION

The issues in this appeal involve whether a person of skill in the art would reasonably understand claim 17 and whether the Mauskop reference, which does not teach or suggest the claimed compound of tramadol hydrochloride and diclofenac sodium anticipates claims 17 or renders claim 38 obvious. The proper reading of the claim language is to a *compound* of tramadol hydrochloride and diclofenac sodium and not a simple *mixture* of these ingredients. The Examiner's reading of the claims to cover a simple mixture of tramadol hydrochloride and diclofenac sodium is beyond any reasonable interpretation of the claim language. The Mauskop reference describes only simple mixtures. Moreover, the declaration evidence already of record in the application convincingly establishes that a compound of tramadol hydrochloride and diclofenac sodium is formed in accordance with the inventive teachings of this application and also that this compound has unexpected a surprising properties when compared against simple mixtures of the active ingredients. Accordingly, the claims are novel and non-obvious over this reference. In view of the foregoing, Applicants respectfully request that the Board reverse the Final Rejections under 35 U.S.C. §112, second paragraph and 35 U.S.C. §§ 102 and 103 and allow claims 17 and 38.

This Appeal Brief is accompanied by a credit card authorization in the amount of $510.00 in payment of the required appeal fee. This amount is believed correct, however, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 05-1323 (Ref Docket No: 029310.50932US).

Respectfully submitted,

December 12, 2007

/Christopher T. McWhinney/

Christopher T. McWhinney
Registration No. 42,875

J. D. Evans
Registration No. 26,269

CROWELL & MORING LLP
Intellectual Property Group
P.O. Box 14300
Washington, DC 20044-4300
Telephone No.: (202) 624-2500
Facsimile No.: (202) 628-8844
JDE:CTM

CLAIMS APPENDIX 37 C.F.R. § 41.37(C)(1)(VIII))

The claims involved in this appeal are as follows:

17. A sustained-release, oral pharmaceutical formulation of tramadol, comprising a compound of tramadol hydrochloride and diclofenac sodium, wherein said compound is formed in situ, said compound having a water solubility of ≤100 mg/ml, and wherein at least part of the tramadol and at least part of the diclofenac are released at the same rate.

38. A method for preparing an oral pharmaceutical formulation, the method comprising:

mixing tramadol hydrochloride and diclofenac sodium to form a mixture;

moistening the mixture; and

repeating the above mixing and moistening steps and formulating the mixture under an energy input.

EVIDENCE APPENDIX 37 C.F.R. § 41.37(C)(1)(IX))

Exhibit I: Applicants rely on the attached Exhibit I, which is a copy of the Declaration of Dr. Iris Ziegler under 35 U.S.C. § 1.132 dated December 14, 2006 and submitted December 15, 2006. Exhibit I is already of record in the present case.

RELATED PROCEEDINGS APPENDIX (37 C.F.R. § 41.37(C)(1)(X))

None

Exhibit I

Declaration of Dr. Iris Ziegler under 35 U.S.C. § 1.132

Originally Submitted: December 15, 2006

Dated: December 14, 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Title	: Oral Pharmaceutical Forms of Administration with a Delayed Action		

DECLARATION OF IRIS ZIEGLER UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Iris Ziegler, hereby declare as follows:

1. I am a citizen of the Federal Republic of Germany residing at Im Dickenbruch 4, D-52159, Roetgen, Germany.

2. I studied pharmacy at the University of Munich and received PhD degree in pharmaceutical technology in the year 1996.

3. Since 1996 I have been employed as a research pharmacist in the field of pharmaceutical technology, and I have been employed in this field by Gruenenthal GmbH of Aachen, Germany since 1997.

4. I am one of the inventors of the invention disclosed and claimed in the above-identified United States patent application no. 10/084,676, and I make this Declaration in support of said patent application.

5. The following tests were carried out in the Laboratories of Gruenenthal GmbH under my supervision and direction.

I(a). Preparation of Tablets containing a mixture of Diclofenac-sodium and Tramadol-hydrochloride according to US 5,914,129.

Tablets having the following composition were prepared by direct compression:

Composition	Amount
Diclofenac-sodium	50.0 mg
Tramadol-hydrochloride	75.0 mg
Microcrystalline cellulose (Avicel PH 101, FMC)	37.5 mg
Colloidal microcrystalline cellulose (Avicel RC591, FMC)	37.5 mg
Lactose monohydrate	50.0 mg
Crospovidone (Kollidon CLM, BASF)	22.5 mg
Microcrystalline cellulose & lactose monohydrate (Cellactose, Meggle)	256.0 mg
Magnesium stearate	1.4 mg
Total weight	529.9 mg

In order to produce the tablets, the Diclofenac-sodium, Tramadol-hydrochloride and the other substances listed above were screened through a 0.6 mm screen and then mixed for 10 minutes in a blender. The resulting blended mixture was compressed on a Korsch EKO tablet press having a 15 x 6 mm die into oblong tablets each weighing 529.9 mg. The resulting tablets containing a mixture of Diclofenac-sodium and Tramadol-hydrochloride had a hardness of approximately 100N, and the disintegration time of the tablets was 5 minutes.

I(b) Preparation of Tablets containing an *in situ* Compound of Diclofenac-sodium and Tramadol-hydrochloride according to Application no. 10/084,676.

(i) Pellets containing an *in situ* formed compound of Diclofenac-sodium and Tramadol-hydrochloride were prepared from the following composition:

Composition	Amount
Diclofenac-sodium	50.0 mg
Tramadol-hydrochloride	75.0 mg
Microcrystalline cellulose (Avicel PH 101, FMC)	37.5 mg
Colloidal microcrystalline cellulose (Avicel RC591, FMC)	37.5 mg
Lactose monohydrate	50.0 mg
Total weight	250.0 mg

In order to produce the *in situ* compound, the Diclofenac-sodium, Tramadol-hydrochloride and the other substances listed above were homogeneously mixed in a Kenwood Chef mixer for 10 minutes and then granulated with water in an amount sufficient for moistening. The resulting sticky, lumpy mass of granules was then extruded in a Nica Type E140 extruder with a 1.0 mm extrusion die. The rods of extrudate were initially extremely sticky but changed in the course of the extrusion process to a very dry extrudate with insufficient plasticity for subsequent spheronization. The extrudate was moistened and granulated again, and the resulting granules were extruded again in the Nica extruder. The moist extrudate was then converted to round pellets of uniform size in a Nica Type S450 spheronizer. The round pellets were dried in a drying cabinet at a temperature of approximately 50°C and then fractionated into sieve fractions.

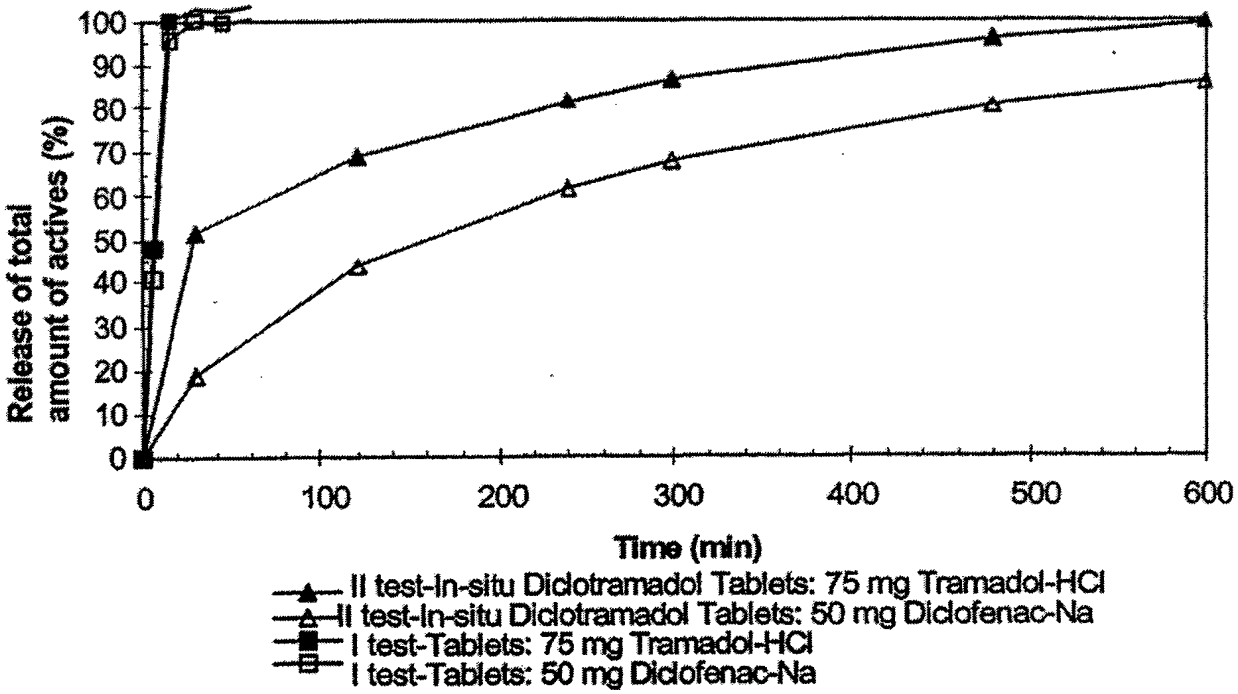
(ii) Tablets having the following composition were then prepared by direct compression:

Composition	Amount
Pellets from step (i) above containing *in situ* compound	250.0 mg
Crospovidone (Kollidon CLM, BASF)	22.5 mg
Microcrystalline cellulose & lactose monohydrate (Cellactose, Meggle)	256.0 mg
Magnesium stearate	1.4 mg
Total weight	529.9 mg

In order to produce the tablets, 250 mg of a 0.63 – 0.8 µm sieve fraction of the pellets from step (i) and the other ingredients listed above were compressed on a Korsch EK0 tablet press having a 15 x 6 mm die into oblong tablets each weighing 529.9 mg. The resulting tablets containing the *in situ* formed compound of Diclofenac-sodium and Tramadol-hydrochloride had a hardness of 60 – 80N, and the disintegration time of the tablets was less than 5 minutes.

I(c) Determination of Active Ingredient Release Profiles

The release profiles of Diclofenac and Tramadol from the tablets containing a mixture of Diclofenac-sodium and Tramadol-hydrochloride obtained in I(a) and the tablets containing an *in situ* formed compound of Diclofenac-sodium and Tramadol-hydrochloride obtained in I(b) above were determined by HPLC as described on page 11 of application no. 10/084,676 in 900 ml of simulated intestinal fluid (pH 7.2) at a rotational speed of 50 rpm. The results are shown in the following graph:



I(d) Discussion

Notwithstanding the fact that the tablets of I(a) and I(b) were identical in size and shape and were made from identical amounts of the same raw ingredients and differed only in their manner of processing, the tablets of I(a) which contained a mixture of Diclofenac-sodium and Tramadol-hydrochloride exhibited a significantly different release profile of both active substances than the tablets of I(b) which contained the *in situ* formed compound of Diclofenac-sodium and Tramadol-hydrochloride. The tablets of I(a) which contained a mixture of Diclofenac-sodium and Tramadol-hydrochloride exhibited a fast release of 100% of both active ingredients within approximately 15 minutes. In contrast thereto, 600 minutes were required to release 100% of the Tramadol and approximately 85% of the Diclofenac from the tablets of I(b) containing the inventive, *in situ* formed compound of Diclofenac-sodium and Tramadol-hydrochloride. The fact that the tablets of I(a) and I(b) exhibited similar hardness and disintegration

times shows that the slower release from I(b) is not attributable to different physical characteristics of the tablets. Rather, the slower release profiles from the tablets of I(b) demonstrate that the Diclofenac and Tramadol in the tablets of I(b) are present in a physical/chemical form (i.e., a lower solubility compound) which is clearly different from the mixture contained in the tablets of I(a).

6. The existence of an *in situ* formed compound of Diclofenac-sodium and Tramadol-hydrochloride in the tablets of I(b) produced according to the present invention is further demonstrated by Differential Scanning Calorimetry (DSC) thermal analyses which were carried out according to my directions. All DSC thermal analyses were performed in the Analytical Chemistry Department of Gruenenthal GmbH using the following parameters:

- using a 40 µl crucible with a perforated cap;
- heating from 30.0°C to 320°C at a rate of 10°C per minute, and;
- flushing with nitrogen gas at 50 ml per minute.

The results of each differential scanning calorimetry scan were plotted with a chart recorder such that endothermic events, such as the melting of individual constituents of the test substances, were indicated by upwardly directed peaks on each plot.

II(a) Tablets obtained in I(a) above containing a mixture of Diclofenac-sodium and Tramadol-hydrochloride were crushed and subjected to DSC as described above. The results are shown in the diagram attached as **Exhibit A.**

II(b) Pellets obtained in I(b)(i) above containing the *in situ* formed compound of Diclofenac-sodium and Tramadol-hydrochloride were also crushed and subjected to DSC as described above. The results are shown in the diagram attached as **Exhibit B.**

II(c) Since Diclofenac-sodium and Tramadol-hydrochloride can react to form a salt of Tramadol and Diclofenac, a further test was carried out to demonstrate that the *in situ* formed compound of Diclofenac-sodium and Tramadol-hydrochloride was not the salt of Tramadol and Diclofenac.

(i) The salt of Tramadol and Diclofenac was prepared by dissolving equimolar amounts of Tramadol-hydrochloride and Diclofenac-sodium in separate water solutions. The two solutions were then mixed together under stirring and then cooled to precipitate the salt of Tramadol and Diclofenac, which was isolated and purified with ethanol by conventional methods.

(ii) The recovered and purified salt was then formulated into pellets having the following composition:

Composition	Amount
Salt of Tramadol and Diclofenac	125.0 mg
Microcrystalline cellulose (Avicel PH 101, FMC)	37.5 mg
Colloidal microcrystalline cellulose (Avicel RC591, FMC)	37.5 mg
Lactose monohydrate	50.0 mg
Total weight	250.0 mg

as described in I(b)(i) above, except that the wet mass was only granulated and extruded once prior to spheronization.

(iii) Pellets obtained in II(c)(ii) above containing the salt of Tramadol and Diclofenac were also crushed and subjected to DSC as described above. The results are shown in the diagram attached as **Exhibit C**.

II(d) To demonstrate that the difference between the DSC analysis of the pellets of I(b)(i) containing the *in situ* formed compound of Diclofenac-sodium and

Tramadol-hydrochloride and the pellets of II(c)(ii) containing the salt of Tramadol and Diclofenac was not caused by the presence of sodium chloride (NaCl), 500 mg of the crushed pellets of II(c)(ii) containing the salt of Tramadol and Diclofenac were admixed with 26.25 mg of NaCl, and the resulting mixture was subjected to DSC as described above. The results are shown in the diagram attached as **Exhibit D**.

II(e) To exclude the possibility that the results of the DSC analysis were influenced by the tabletting process of I(a), a sample of the blended mixture prior to tabletting was also subjected to DSC analysis. The results are shown in the diagram attached as **Exhibit E**.

II(f) Discussion

By comparing the two scans of **Exhibits A and B** the existence of a pronounced peak in **Exhibit B** at approximately 292°C, which has no counterpart in the scan of **Exhibit A** is evident. This peak shows the presence of a chemical entity in the pellets of I(b)(i) produced according to the present invention which is not present in the tablets of I(a) produced according to the teachings of Mauskop, US 5,914,129.

The difference between the scans of **Exhibits B and C** indicates that the product of the present invention is not the salt of Tramadol and Diclofenac since that pronounced peak in **Exhibit B** at approximately 292°C is missing in **Exhibit C**.

The essential similarity between the scan of **Exhibit C**, which shows the DSC analysis of the salt of Tramadol and Diclofenac, and the scan of **Exhibit D**, in which sodium chloride is added, establishes that the difference between the scans of **Exhibits B and C** is not attributable to the presence of sodium chloride which may form during the process.

Finally, the essential similarity between the scan of **Exhibit A**, which shows the result of a DSC scan of a tablet containing a mixture of Diclofenac-sodium and Tramadol-hydrochloride, and the scan of **Exhibit E**, which shows the result of a

scan of a blended powder mixture containing Diclofenac-sodium and Tramadol-hydrochloride, establishes that the tabletting process does not change the DSC results.

7. The different release profiles of the Tramadol and Diclofenac from the tablets of I(b) produced according to the present invention compared to the tablets of I(a) produced according to the teachings of Mauskop, US 5,914,129 containing a mixture of Diclofenac-sodium and Tramadol-hydrochloride, are indicative of a significant difference in solubility and demonstrate that the Diclofenac and Tramadol must be present in a physical/chemical form which is different from a mixture as taught by Mauskop. The different differential scanning calorimetry results of the pellets of I(b)(i) produced according to the present invention compared to the tablets of I(a) containing a mixture of Diclofenac-sodium and Tramadol-hydrochloride according the teachings of Mauskop, US 5,914,129, and particularly the endothermic peak at approximately 292°C which has no counterpart in the DSC of the crushed tablets of I(a), corroborate the presence of a different physical/chemical species in the product of the present invention which is not present in the tablets containing a mixture of Diclofenac-sodium and Tramadol-hydrochloride as taught by Mauskop. These results evidence that the product of the present invention contains an *in situ* formed compound of Diclofenac-sodium and Tramadol-hydrochloride which is not present in the tablets containing a mixture of Diclofenac-sodium and Tramadol-hydrochloride as taught by Mauskop.

8. All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true, and further, these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements

may jeopardize the validity of this patent application or any patent issued thereon.

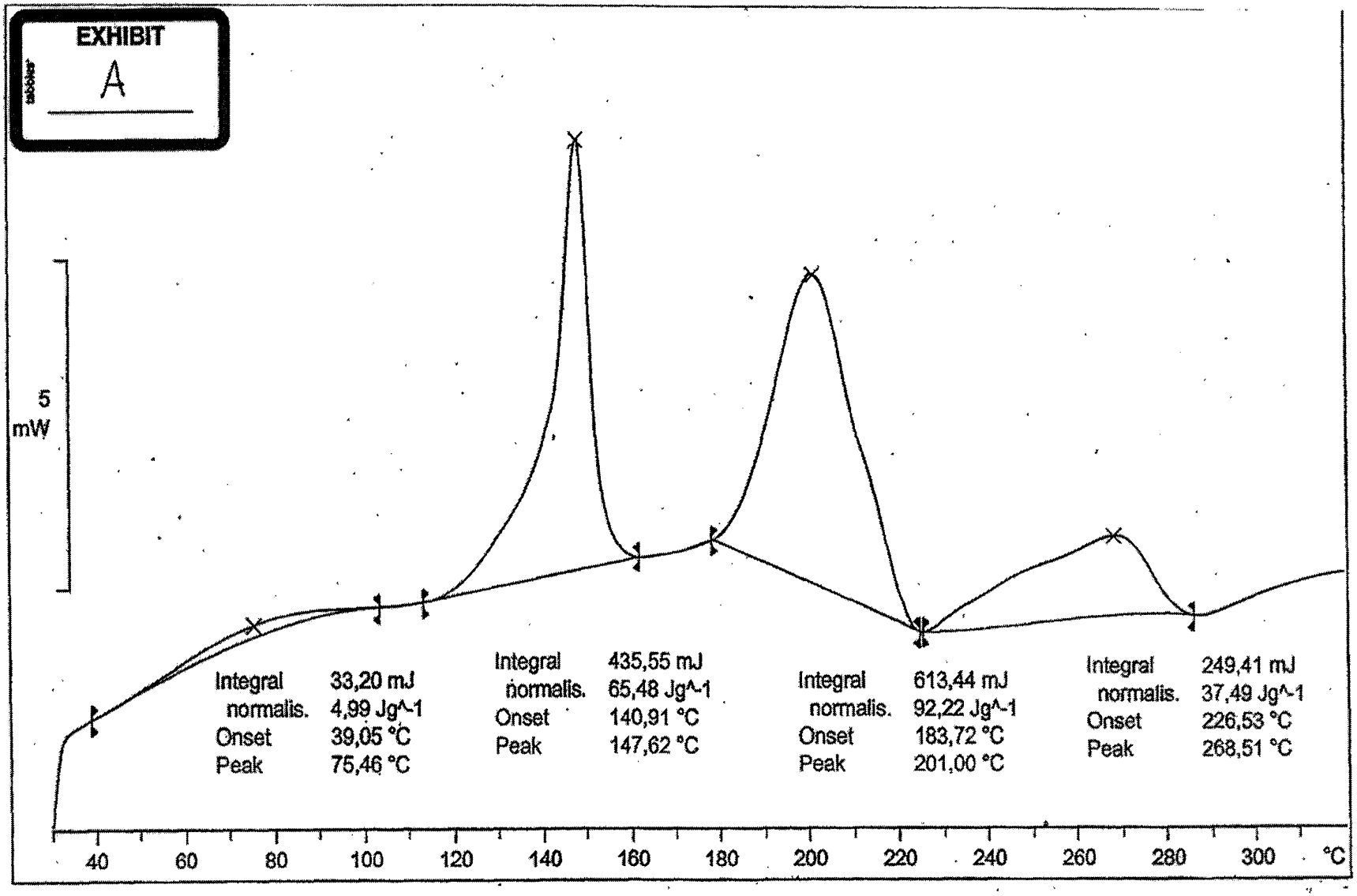
Date: 14 Dec 2006

I. Ziegler

Iris Ziegler

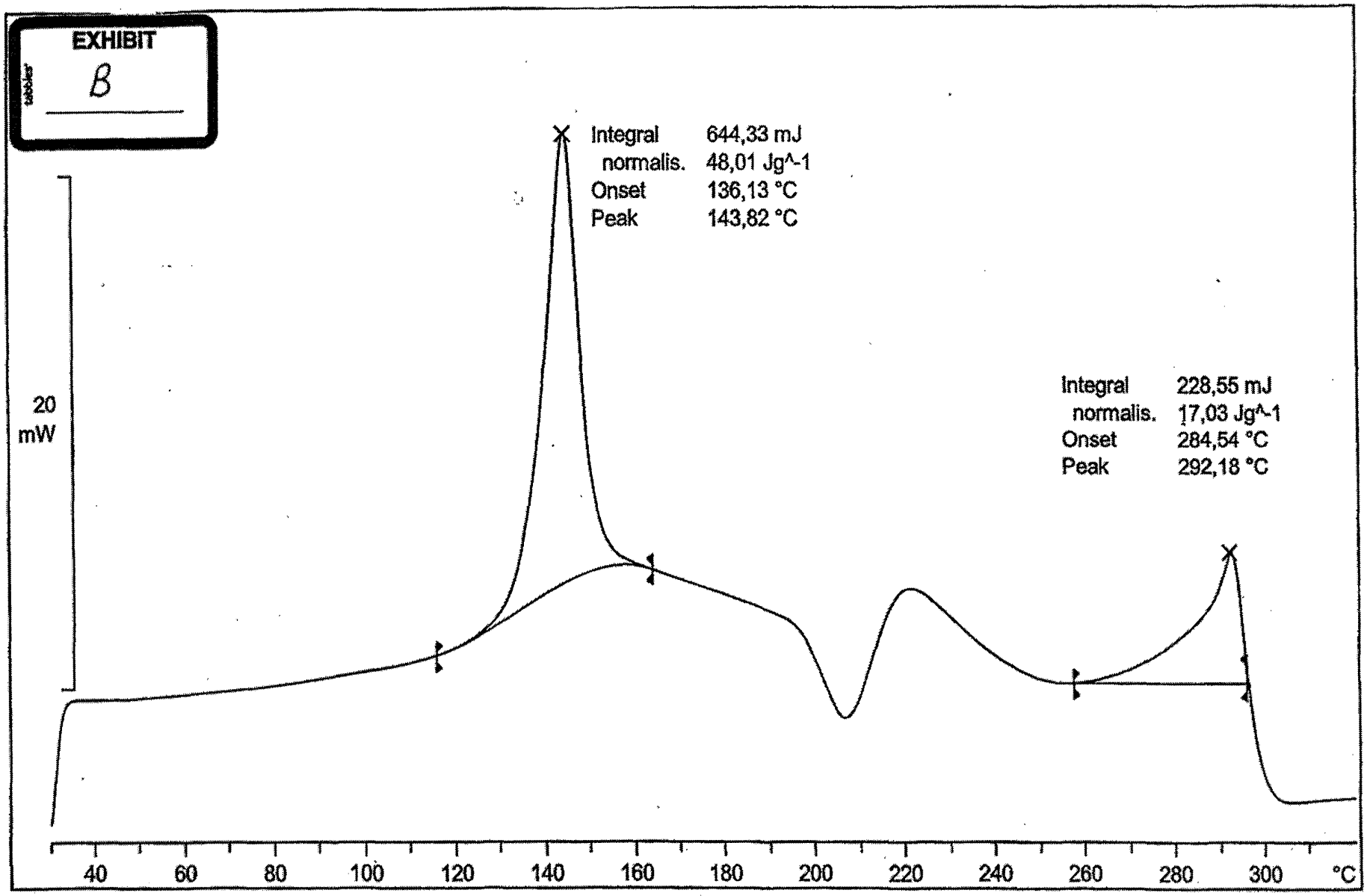
Crushed Tablets containing Blended Powder containing Tramadol-HCl and Diclofenac-Na

EXHIBIT
A

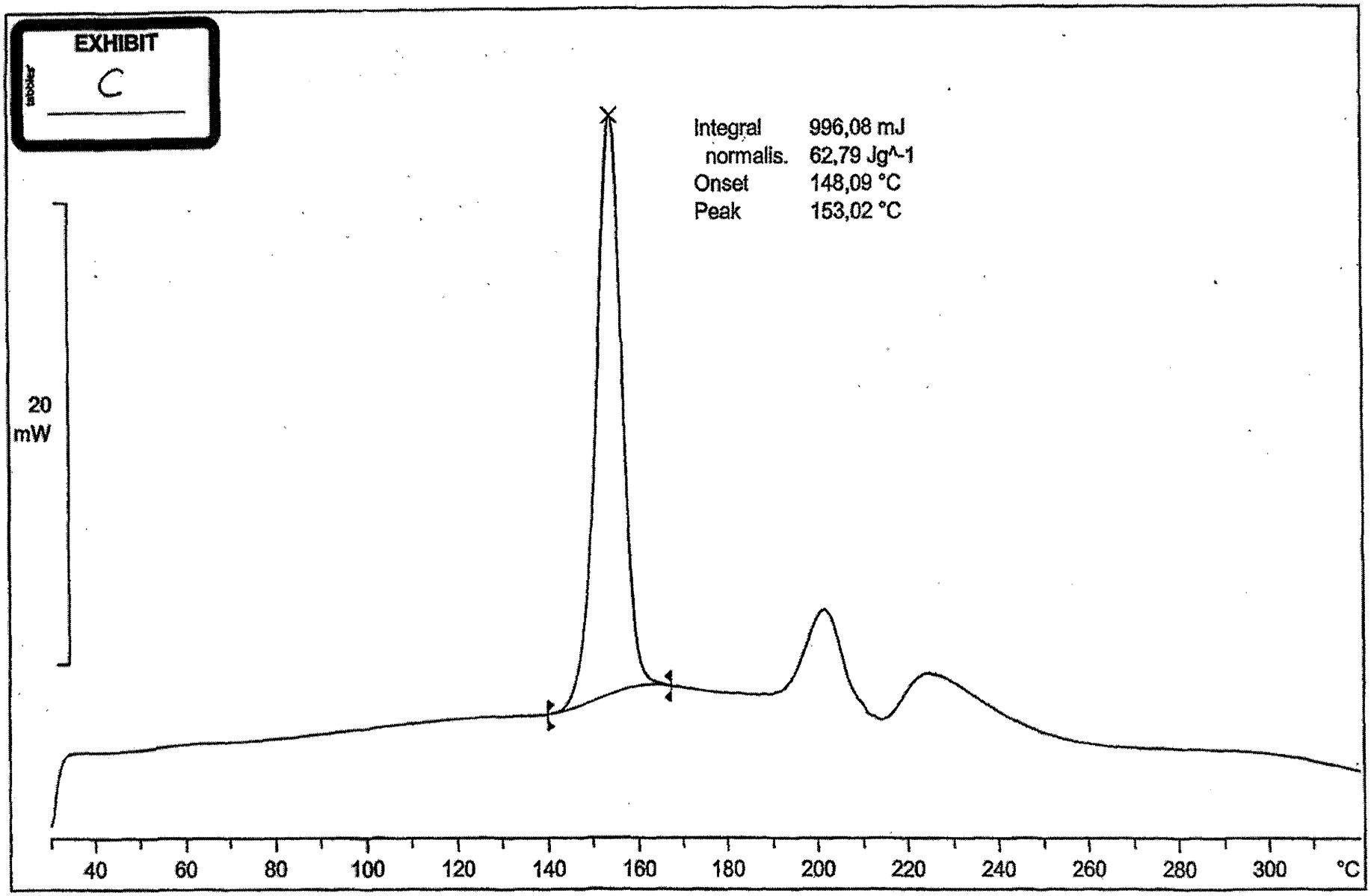


Crushed Pellets containing *in situ* formed Compound of Tramadol- HCl and Diclofenac-Na

EXHIBIT
B

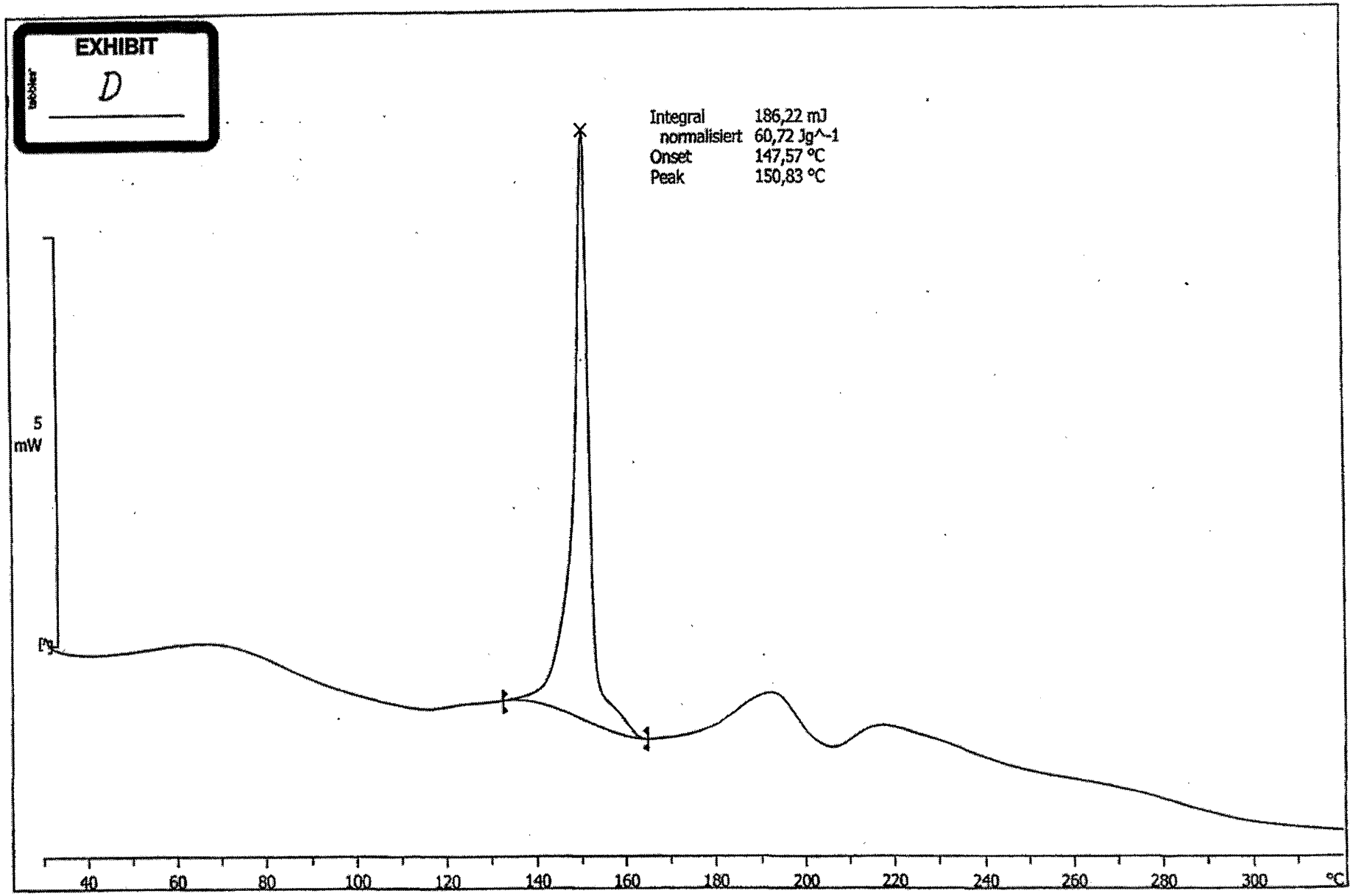


Crushed Pellets containing Salt of Tramadol and Diclofenac



Crushed Pellets containing Salt of Tramadol and Diclofenac and Added NaCl

EXHIBIT
D



Blended Powder containing Tramadol-HCl and Diclofenac-Na

EXHIBIT
E